REMARKS

Claims 1-6, 8, 9, 11-25, 31-33, 35 and 36 are pending in this application. Claims 7, 10, 26-30 and 34 are canceled. Claims 6, 9 and 14 are withdrawn from further consideration as being drawn to a nonelected species. Upon allowance of the generic claim, applicant will request rejoinder of claims 6, 9 and 14.

Applicants have canceled claim 7, 10, 26-30 and 34 without prejudice and without waiver of their right to file for and obtain claims directed to any canceled subject matter in divisional and continuing applications which claim priority from this application.

Applicants have amended claims 1, 17, 23 and 31 to more clearly recite what the applicants consider their invention by canceling the recitation of the source of the osteogenic protein. Support for this amendment is provided, e.g., on page 2, lines 24-25; page 27, line 22 to page 29, line 16; page 32, lines 13-18; and page 43, lines 8-13 of the specification.

Applicants have amended claims 1, 32 and 35 to recite a non-polymeric, non-synthetic matrix selected from the

group selected from collagen, apatites, hydroxyapatites, tricalcium phosphates, and admixtures thereof. Support for this amendment may be found on page 5, lines 5-8; page 7, lines 12-15; and page 18, lines 4-7 of the specification.

Applicants have amended claims 1, 32 and 35 to recite a binding agent selected from the group consisting of cellulose, and salts thereof. Support for this amendment may be found on page 7, lines 20-22; and page 26, lines 21-26 of the specification.

Applicants have amended claims 1, 17, 31, 32 and 35 to recite that the binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90. Support for this amendment may be found on page 48, line 4 to page 49, line 9 of the specification.

Applicants have amended claims 20 and 23 to depend from claim 1.

Applicants have amended claims 20-24 to recite that the binding agent to matrix ratio is "x" parts by weight binding agent to "y" parts by weight matrix. Support for this amendment may be found on page 8, line 22 to page 9, line 9 of the specification.

None of the amendments adds new matter.

Applicants have amended claim 32 to recite a first and second receptacle. Support for this amendment may be found on page 10, lines 10-16 of the specification.

Applicants address the Examiner's rejection below:

35 U.S.C. § 103(a)

Claims 1-5, 7, 8, 11-13 and 31

The Examiner has rejected claims 1-5, 7, 8, 11-13 and 31 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent 5,422,340 ("Ammann") and U.S. Patent 5,597,897 ("Ron"). The Examiner states that Ammann discloses a formulation suitable for inducing bone formation that contains about 0.5 μg to about 5 mg of transforming growth factor-β and about 140 mg to about 50 g of tricalcium phosphate and a polymer for enhancing consistency of the formulation, which may be any polysaccharide or insoluble protein material useful for binding the TGF-β to the TCP to form a smooth, moldable putty or paste, such as carboxymethyl cellulose and collagen, or a combination of these. The Examiner states that Ammann does not teach a binding agent with a degree of substitution of

0.65-0.90. The Examiner states that Ron discloses pharmaceutical formulations designed to sequester osteogenic proteins *in situ* for a time sufficient to allow the protein to induce cartilage and/or bone formation, wherein the osteogenic proteins are BMPs 1-8 wherein the osteogenic protein-sequestering material is carboxymethylcellulose with a 0.7 degree of substitution. The Examiner also states that Ron does not teach a pharmaceutical formulations comprising TCP. However, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to make a formulation suitable for inducing bone formation that contains TGF-β, TCP, carboxymethylcellulose and collagen, as taught by Ammann and to modify this teaching by using CMC with a 0.7 degree of substitution, as taught by Ron, with a reasonable expectation of success. The Examiner further states that one of skill in the art would be motivated to make this modification in order to sequester osteogenic proteins in situ for a time sufficient to allow the protein to induce cartilage and/or bone formation. Furthermore, the Examiner states that it would have been obvious to one of skill in the art to substitute osteogenic proteins of the BMP family identified as BMP-1 through BMP-8, as taught by Ron, in

the formulation, as taught by Ammann, with a reasonable expectation of success and that the skilled worker would be motivated to make this modification because he would have a reasonable expectation that either osteogenic proteins of the BMP family identified as BMP-1 through BMP-8 or TGF-β would perform their expected function.

Applicants have amended claims 1 and 31 (and therefore dependent claims 2-5, 8 and 11-13) to recite a device for inducing local bone or cartilage formation comprising an osteogenic protein, a non-synthetic, non-polymeric matrix selected from the group consisting of collagen, apatites, hydroxyapatites, tricalcium phosphates and admixtures thereof, and a binding agent selected from cellulose, and salts thereof, wherein said binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90.

Ammann discloses a bone-inducing formulation comprising TGF-β and TCP and optionally, a polymer for enhancing consistency of the formulation useful for binding the TGF-β to the TCP to form a smooth, moldable putty or paste. First, applicants respectfully submit that TGF-β is

not encompassed by applicants' defined genus of osteogenic proteins. The present invention contemplates a class of proteins which can induce the full cascade of morphogenic events including formation of cartilaginous intermediates, culminating in the formation of new endochondral bone. See pages 2 and 23-24 of the specification. TGF-β does not fall within this definition. Second, Ammann does not disclose a device for inducing local bone or cartilage formation comprising *inter alia* an osteogenic protein as defined in the instant application and a binding agent selected from cellulose or admixtures thereof, wherein said binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90. This deficiency is not remedied by Ron. Ron discloses a composition comprising an osteogenic protein selected from BMPs 1-8, a polymer matrix and an osteogenic protein sequestering material including cellulose. However, Ron does not teach or suggest a binding agent having a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90 as claimed in the instant application. Rather, the carboxymethylcellulose of Ron has a viscosity of 2480 cps (see column 6, lines 39-41). Accordingly, Ammann and Ron, either alone or in combination, does not teach or suggest the device

of claims 1-5, 7, 8, 11-13 and 31. Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

Claims 1, 15, 16, 32, 33, 35 and 36

The Examiner has rejected claims 1, 15, 16, 32, 33, 35 and 36 under 35 U.S.C. § 103(a) as being obvious over Ammann and Ron in view of Arnaud E. et al., "Potentiation of transforming growth factor (TGF-beta 1) by natural coral and fibrin in a rabbit cranioplasty model", *Calcif. Tissue Int.*, Vol. 54(6), pp. 493-498 (1994)("Arnaud") and Turco, S. J. et al., "Intravenous Admixtures", Chapter 85 in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Pub. Co., Easton, Pennsylvania, p. 1570 (1990)("Turco"). The Examiner states that Arnaud discloses that the association of TGF-β1 in fibrin and coral induces bone growth and teaches preparations of TGF-β1 in saline for making the composite and that Turco teaches that proper electrolyte concentration and balance in plasma and tissues are critical for proper body function and that the electrolytes in normal saline are more closely approximate the composition of the extracellular fluid than solutions of any other single salt. The Examiner, therefore, concludes that it would have been obvious to one skilled in the art to arrive at

an osteogenic device comprising CMC, as taught by Ammann and Ron, and to modify that teaching by making a device comprising saline, as taught by Arnaud and Turco with a reasonable expectation of success. The Examiner states that one of skill in the art would be motivated to make this modification because preparing OP-1 in saline would allow one of ordinary skill in the art to adjust the concentration of OP-1 so that an appropriate amount of OP-1 could be added to the device and the desired concentration of OP-1 in the device could be achieved and because the electrolytes in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt. Finally, the Examiner states that it would have been obvious to one of ordinary skill in the art to house the osteogenic protein agent, matrix agent, binding agent and wetting agent in separate receptacles or combinations of agents in the same receptacle with a reasonable expectation of success.

Amended claims 1, 15 and 16 recite a device for inducing local bone or cartilage formation comprising an osteogenic protein, a non-polymeric, non-synthetic matrix selected from collagen, apatites, hydroxyapatites, tricalcium phosphates, and admixtures thereof, and a binding agent

selected from cellulose, and salts thereof, wherein said binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90. Amended claims 32 and 35 (and therefore, dependent claims 33 and 36) recite a kit for inducing local bone or cartilage formation comprising receptacles to house an osteogenic protein, a non-polymeric, non-synthetic matrix selected from collagen, apatites, hydroxyapatites, tricalcium phosphates, and admixtures thereof, and a binding agent selected from cellulose and salts thereof, wherein said binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90.

As discussed above, Ammann discloses a bone-inducing formulation comprising TGF-β and TCP and optionally, a polymer for enhancing consistency of the formulation useful for binding the TGF-β to the TCP to form a smooth, moldable putty or paste. The TGF-β of Ammann is not encompassed by the genus of osteogenic proteins as defined in the specification. Ammann also does not disclose a device or kit for inducing local bone or cartilage formation comprising an osteogenic protein, a non-synthetic, non-polymeric matrix selected from the group consisting of collagen, apatites, hydroxyapatites,

tricalcium phosphates and admixtures thereof, and a binding agent selected from cellulose and salts thereof, wherein said binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90, as recited in the amended claims. None of Ron, Arnaud and Turco remedy this deficiency. None of these references recite such a matrix and binding agent combination. Ron discloses a composition comprising an ostegenic protein, a polymer matrix and an osteogenic protein sequestering material. Arnaud discloses TGF-β1 compositions in combination with methylcellulose, fibrin glue and/or natural coral skeleton. Turco discloses intravenous fluids and their components including electrolyte concentration. None of these references, alone or in combination, disclose a non-synthetic, non-polymeric matrix selected from the group consisting of collagen, apatites, hydroxyapatites, tricalcium phosphates and admixtures thereof, and a binding agent selected from cellulose, and salts thereof, wherein the binding agent has a viscosity of about 10-200 cP and a degree of substitution of 0.65-0.90. Accordingly, Ammann, Ron, Arnaud and Turco taken together do not teach or suggest a device or kit of claims 1, 15, 16, 32, 33, 35 and 36.

Accordingly, applicants request that the Examiner withdraw this obviousness rejection.

35 U.S.C. § 112, 1st Paragraph

Claims 1, 7-9, 11-16, 20-22, 32, 33, 35 and 36

The Examiner has rejected claims 1, 7-9, 11-16, 20-22, 32, 33, 35 and 36 under 35 U.S.C. § 112, first paragraph for lack of written description. Specifically, the Examiner contends that the recitation of "an osteogenic protein" lacks written description. The Examiner states that the specification and claim do not indicate what distinguishing attributes are shared by the members of the genus and no common structural attributes identify the members of the genus. The Examiner states that one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus and thus, applicants were not in possession of the claimed genus. Applicants traverse.

Applicants respectfully submit that the disclosure provides ample written description for the term "osteogenic protein." The specification at page 23, line 20 to page 25, line 20 defines "osteogenic proteins" as proteins which can

induce the full cascade of morphogenic events culminating in endochondral bone formation. The specification describes that these proteins share common structural features including processing from a precursor "pro-form" to yield a mature polypeptide chain competent to dimerize and containing a carboxy terminal active domain of approximately 97-106 amino acids (see, e.g., page 2. lines 6-10). In addition, members of this family of proteins share a conserved pattern of cysteines in this active domain and can be disulfide bonded to form dimers (see, e.g., page 2, lines 10-12). The specification provides numerous examples of such proteins (see, e.g., page 23, line 22 to page 25, line 25; see also page 30, line 7 to page 43, line 13), including biosynthetic osteogenic proteins, such as mutants and chimeric proteins (see, page 25, lines 16-20). Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 1-9, 11-16, 32, 33, 35 and 36

The Examiner has rejected claims 1-9, 11-16, 32, 33, 35 and 36 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner states that the limitation "the device does not comprise a demineralized bone matrix" can not be found in the disclosure, as originally filed, and the

introduction of such a limitation raises the issue of new matter.

Applicants have amended claims 1, 32 and 35 (and therefore the claims dependent therefrom) to recite a non-synthetic, non-polymeric matrix selected from the group consisting of collagen, apatites, hydroxyapatites, tricalcium phosphates, and admixtures thereof. Support for this amendment is provided at page 5, lines 5-8; page 7, lines 12-15; and page 18, lines 4-7 of the specification. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 112, 2nd Paragraph

Claims 1-9, 11-25, 31-33, 35 and 36

The Examiner has rejected claims 1-9, 11-25, 31-33, 35 and 36 under 35 U.S.C. § 112, second paragraph, contending that the recitation of "naturally occurring sources" is indefinite.

Applicants have amended claims 1, 17, 31, 32 and 35 (and therefore, dependent claims 2-6, 8, 9, 11-16, 18, 19, 20-25, 33 and 36) to delete the recitation of the source of the osteogenic protein. Support for this amendment is provided at page 2, lines 24-25; page 27, line 22 to page 29, line 16;

page 32, lines 13-18; and page 43, lines 8-13 of the specification. Accordingly, the Examiner's rejection has been obviated.

Claims 1-9, 11-16, 32, 33, 35 and 36

The Examiner has rejected claims 1-9, 11-16, 32, 33, 35 and 36 under 35 U.S.C. § 112, second paragraph, stating that the term "synthetic polymer matrix" is indefinite.

Applicants have amended claims 1, 32 and 35 (and therefore, dependent claims 2-6, 8, 9, 11-16, 33 and 36) to recite a non-synthetic, non-polymeric matrix selected from the group consisting of collagen, apatites, hydroxyapatites, tricalcium phosphates, and admixtures thereof. Support for this amendment is provided at page 5, lines 5-8; page 7, lines 12-15; and page 18, lines 4-7 of the specification. Applicants believe that the claims as amended are definite. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 1-9, 11-25, 31-33, 35 and 36

The Examiner has rejected claims 1-9, 11-25, 31-33, 35 and 36 under 35 U.S.C. § 112, second paragraph, stating that the recitation of "viscosity of about 10-200 cP" is

indefinite because viscosity of cellulosic materials depends on the concentration. Applicants traverse.

Applicants respectfully submit that the recitation of viscosity in claims 1-9, 11-25, 31-33, 35 and 36 is definite. One of skill in the art would readily be able to determine the viscosity of the binding agent using various methods available in the art (see, e.g., Bulletin VC-453C cited by the Examiner and attached to the June 30, 2003 Office Action). Applicants further submit that numerous factors, other than concentration, affect the viscosity of any given material. In fact, the document that the Examiner cites recites various factors other than concentration which affect viscosity. These include, but are not limited to, the degree of aggregation of the binding agent, the nature and composition of the solvent and the solutes used. Applicants believe that it is not necessary to recite all the factors that affect the viscosity. A recitation of the specific viscosity is sufficient because the skilled worker can easily ascertain that parameter using methods known in the art. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 1-5, 7, 8, 15, 16, 20-24, 32, 33, 35 and 36

The Examiner has rejected claims 1-5, 7, 8, 15, 16, 20-24, 32, 33, 35 and 36 under 35 U.S.C. § 112, second paragraph because the term "derivatives thereof" is indefinite.

Applicants have amended the claims to recite that the binding agent is cellulose and salts thereof. Support for this amendment is provided , e.g., at page 44, lines 13-23 of the specification. Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 2 and 3

The Examiner has rejected claims 2 and 3 under 35 U.S.C. § 112, second paragraph because the term "variants" is indefinite. Applicants traverse.

Applicants respectfully submit that the term "variants" is clearly defined in the specification. The specification, at page 23, line 20 to page 25, line 18 and at pages 27-43 describe the osteogenic proteins of the instant invention and what is intended by the term "variant." The specification defines that the osteogenic proteins must be able to induce the full cascade of morphogenic events

culminating in endochondral bone formation. The specification also recites that the osteogenic protein may be a protein that share 70% homology with a reference sequence, wherein 70% of the aligned residues are identical to or are conservative variants of the corresponding residue in a reference sequence. The specification further describes what the variations may be (see, e.g., page 24, lines 20-26; page 29, lines 17-24; and page 31, lines 18 to page 32, line 20). Accordingly, applicants request that the Examiner withdraw this rejection.

Claims 32, 33, 35 and 36

The Examiner has rejected claims 32, 33, 35 and 36 under 35 U.S.C. § 112, second paragraph because it is unclear if the "kit" comprises the device of claim 1, or if "for inducing ...using the device of claim 1" is an intended use of the "kit."

Applicants have amended claims 32 and 35 (and therefore dependent claims 33 and 36) to recite a kit for inducing local bone or cartilage formation, thus, obviating the Examiner's rejection.

Claim Objections

Claims 20 and 22-24

The Examiner has objected to claims 20 and 22-24 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner states that the terms "fewer parts" and "fewer than" encompass zero parts and zero parts fails to further limit and does not infringe a part.

Applicants have amended claims 20-23 (and thereby claim 24) to recite that the proportion of matrix or binding agent is "1-'x' parts by weight." Accordingly, applicants request that the Examiner withdraw this objection.

CONCLUSION

In view of the foregoing remarks and amendments, applicants request that the Examiner favorably reconsider this application and allow the claims pending herein. If the Examiner believes that a telephone conference would expedite allowance of this application, he is invited to telephone the undersigned at any time.

Respectfully submitted,

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